EUROPEAN CHEMICALS AGENCY

Helsinki, 24 October 2017

Addressee: [redacted]

Decision number: TPE-D-2114363740-51-01/F
Substance name: Reaction mass of methyl dihydrogen phosphate and orthophosphoric acid and dimethyl hydrogen phosphate
List number: 908-996-7
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 05.05.2015
Registered tonnage band: 100-1000T

## DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined your testing proposal(s) and decided as follows.

While your originally proposed test for Sub-chronic toxicity study (90-day), oral route (EU B.26./OECD TG 408) and Pre-natal developmental toxicity study (EU B.31./OECD TG 414) using the analogue substance phosphoric acid, butyl ester CAS No 12788-93-1 are rejected, you are requested to perform:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats using the registered substance.**
2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rats or rabbits), oral route using the registered substance.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **31 October 2019**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

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**Appeal**

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

**Appendix 1: Reasons**

The decision of ECHA is based on the examination of the testing proposal(s) submitted by you.

## 0. Grouping of substances and read-across approach

The decision of ECHA is based on the examination of the testing proposals submitted by you for the registered substance Reaction mass of methyl dihydrogen phosphate and orthophosphoric acid and dimethyl hydrogen phosphate, (EC no 908-996-7); hereafter referred to as "target substance"), proposed to be performed with a source substance phosphoric acid, butyl ester CAS No 12788-93-1 (EC No 235-826-2) on the submitted read-across justification. ECHA has considered first the scientific validity of the read-across hypothesis (preliminary considerations below), before assessing the testing proposed (sections 1.0 and 2.0, below).

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including from information from structurally related substances (grouping or read-across), "*provided that the conditions set out in Annex XI are met*".

According to Annex XI, 1.5 there needs to be structural similarity among the substances within a group or a category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for reference substance(s) by interpolation, and the data should be adequate for the purpose of classification and labelling and/or risk assessment.

### 0.1 Description of the grouping and read-across approach proposed by you

You have proposed to cover the standard information requirements for a sub-chronic toxicity study (90-days; Annex IX, Section 8.6.2.) and a pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) by performing the test with a source substance phosphoric acid, butyl ester CAS No 12788-93-1 (EC No 235-826-2).

You have provided a hypothesis/justification attached in relevant sections of the IUCLID dossier for each endpoint. You summarise the hypothesis as follows "Due to the similarity of the chemical structure and functional groups and the comparable study results concerning the toxicological endpoints acute oral toxicity, genotoxicity, reproductive/developmental toxicity and repeated dose oral toxicity a read across between the below mentioned organo phosphate esters is considered to be justified."

### 0.2 Information/documentation submitted to support the grouping and read-across hypothesis

You have provided a read-across justification as a separate attachment in the endpoint summary in the registration for each endpoint. The justification is identical for both endpoints. Furthermore, you have included a separate read-across justification in section 13 of the IUCLID dossier.

In the technical dossier you have provided the following studies conducted with the target substance: a combined repeated dose toxicity study with reproduction/developmental toxicity screening done according to OECD guideline 422. You have provided in your dossier a study summary for a dose range finding study for reproductive/developmental toxicity screening test combined with teratogenicity study (OECD TG 422/ OECD TG 414). However, you have not provided in your technical dossier any other repeated dose toxicity or reproductive/developmental toxicity studies conducted with the source substance. Nevertheless, in your attached read-across justification document, you have indicated that a reproduction/developmental toxicity screening done according to OECD guideline 422 has been performed on the source substance. This study is summarised in your justification document as follows

"OECD 422 in rats (Klimisch 2; impurity: 18.3% Phosphor acid, tributyl ester): thickening of mucosa in the forestomach, erosion of gastric mucosa, distended caecum, increased liver weight (effects which are referred to the mono- and diester component); no effects on reproduction observed".

No further information is provided in the technical dossier on this particular study.

Finally, you have provided in the attached justification document brief summaries of a number of toxicological studies, including acute toxicity as well as mutagenicity studies, on the target substance, the source substance, as well as two other substances: Phosphoric acid, mixed esters with Bu alc. and ethylene glycol (EC 284-716-0), and phosphoric acid, hexadecyl ester (CAS No 3539-43-3).

ECHA notes that some of the information on these studies, while not available in this technical dossier, it is nevertheless available in the technical dossier of the source substance(s). While noting this shortcoming, ECHA has taken the information available in the source dossiers into account in its decision on your testing proposal. ECHA notes that you have submitted the same testing proposal in the source substance's dossier, as well as in the dossier for the substance reaction mass of phosphoric acid, mixed esters with Bu alc. and ethylene glycol, CAS No 84962-20-9, (EC 284-716-0).

In your comments to ECHA's draft decision, you provided extensive additional information in support of the read-across approach. These consist of the following key information:

1) A data matrix of physico-chemical, toxicological, and ecotoxicological properties of different phosphate esters, including the source and target substances.
2) Detailed information on the structure and composition of the source and target substances, as well as detailed analytical information including NMR, IR, UV/Vis spectroscopy, gas chromatography, liquid chromatography/mass spectrometry.
3) New *in vitro* toxicokinetic information: this consists of an analysis of the hydrolysis of dibutyl phosphate and myristyl phosphate in cryopreserved human hepatocytes

Based on this information, you conclude the following:

- The Registered substance as well as the source substance (phosphoric acid, butyl ester), and the other target substance (phosphoric acid, mixed esters with Bu alc. and ethylene glycol) and other phosphoric acid esters share a similar structure and show a trend in their physico-chemical properties. They also show similar properties with respect to environmental fate and toxicological properties. The similarity in structure, the trend in physico-chemical properties, and the similarity of toxicological properties support read-across from the source to the target.

- The new *in vitro* studies on the degradation of two phosphate esters (dibutyl phosphate and dimyristyl phosphate) using cryopreserved human hepatocytes show no hydrolysis of the ester bond. You consider that this information addresses the possibility that the different phosphate esters will hydrolyse, leading to different alcohols, which may in turn lead to differences in toxicity between the different phosphate esters. You consider that the toxicity of these substances will be driven by the phosphate ester, and not by any hydrolysis products.
- You consider that the differences in NOAEL among different studies performed with different phosphate esters is due to the differences in the dose-steps, and is not an indication of differences in potency.
- You note that an impurity, tributyl phosphate ester, present in high concentrations (19%) in the OECD TG 422 study on the source substance , is the likely source of bladder effects observed in this study. This impurity is not present in the source substance as it is registered, nor in the target substance.

Based on the above, you conclude that the effects of the target substance can be predicted from the source substance.

However, you also note that there is some uncertainty regarding the proposed read-cross approach, due to the bladder effects observed in the OECD TG 422 study on the source substance. Therefore, you suggest a tiered strategy, as follows: first, to test the phosphoric acid, butyl ester for both the repeated dose toxicity study, and the pre-natal developmental toxicity study. Second, in case effects are observed in these studies that are not typical to phosphate esters (bladder effects, developmental effects), then a sub-chronic toxicity study and/or a pre-natal developmental toxicity study would be performed on the registered substance.

### 0.3 ECHA analysis of the grouping approach and read-across hypothesis in light of the requirements of Annex XI, 1.5.

Based on the information provided, ECHA understands that the proposed read-across hypothesis is based on two main arguments:

1) Structural similarity, similarity of physico-chemical and environmental fate properties and lack of hydrolysis of the ester bond;
2) Similarity in toxicological effects.

Structural similarity and dissimilarity, similarity of physico-chemical and environmental fate properties and lack of hydrolysis of the ester bond

In order to meet the provisions in Annex XI, Section 1.5. to predict human health effects from data for a reference substance within the group by interpolation to other substances in the group, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

You have provided substance identity data, including composition of the target substance. However you have not provided information on the composition of the source substances in the technical dossier of the target substance, while this information is available in the technical dossier of the source substance. You have also provided information on the composition of the source substance in your comments to ECHA's draft decision.

You explain that both substances, as well as the other source substances indicated above, are esters of phosphoric acid with a general structure of P(=O)(OR)3. You have further explained that the substances are a mixture of mono and diesters of phosphoric acid, with unbranched chains (C1, C4, and C16), with the exception of the substance phosphoric acid, mixed esters with Bu alc. and ethylene glycol. This particular substance contains esters of ethylene glycol, in contrast to the other substances cited in your justification, which contain esters of C1, C4, and C16 alcohols.

ECHA notes that based on the available information in the registration dossiers of the source and target substance, as well as the information submitted as part of your comments to the draft decision, there is structural similarity in the source and target substances, as both are esters of phosphoric acid, containing monoesters and diesters.

However, based on the available information, there are also significant differences in the structure and composition of the source and target substances: the target substance is composed of methyl dihydrogen phosphate, dimethyl hydrogen phosphate, as well as 20-55% of orthophosphoric acid. This is in contrast to the source substance, where the esters are butyl esters (mono and diesters, as well as triesters as an impurity). In addition, while phosphoric acid is also present in the source substance, its concentration is significantly lower than that in the target substance.

ECHA notes that in your comments to the draft decision, you have also provided a data matrix of physico-chemical and environmental properties. You consider that this shows a clear trend in these properties depending on the alcohol chain length. You consider that there is a trend in physico-chemical characteristics that might influence the toxicological mode of action. You also consider that the substances show similar properties with respect to environmental fate including hydrolysis and biodegradation.

You conclude based on this information that the source and target substances share a similar structure, and where there are structural differences or variations in composition, that these do not have a substantial impact on the physico-chemical or toxicological properties of the substances.

In addition to the structural similarity and similarity in physico-chemical and environmental properties of the source and target substances, an important point of the assessment of your read-across proposal is whether the ester bond in the source and target substances hydrolyse leading to different metabolites with potentially different toxicological effects. In addition, ECHA observes that the read-across justification document attached in your technical dossier, you also propose to read-across information from another source substance, phosphoric acid, 2-ethylhexyl ester to the target substance to evaluate its metabolic profile. Based on the information available on this particular source substance, you concluded that the ester bond in the target substance may be hydrolysed, and this hydrolysis would be independent of the constituent alcohol part of the molecule. Assuming such hydrolysis occurs, the resulting hydrolysis products would be different between the source and target substances. Specifically, the hydrolysis of the target substance would release methanol. This is in contrast to the source substance, where the hydrolysis can be expected to result in the release of butanol. ECHA highlights that butanol and methanol in themselves may have significant differences in their toxicological properties. You have not considered the potential impact of the structural differences in the hydrolysis products in your read-across justification.

ECHA considers that the structural differences between the source and target substances, and the structural differences between the potential hydrolysis products may have a significant impact on the properties of these substances, and thus on the ability to predict the properties of the target substance from a test performed on the source substance. You have not taken these structural differences into account in your read-across justification. ECHA further notes that based on the available information, these structural differences result in some differences in the toxicological properties of the substances, as seen below.

In your comments to the draft decision, you have reconsidered this conclusion. First, you note that the source and target substances do not undergo hydrolysis in hydrolysis studies for the environment (hydrolysis as a function of pH). Furthermore, you submitted information from an *in vitro* studies examining the degradation of two substances: dibutyl phosphate and dimyristyl phosphate in cryopreserved human hepatocytes. These studies examined the formation of the alcohol metabolites butanol and 1-tetradecanol from dibutyl phosphate and dimyristyl phosphate in this test system. The results showed no formation of the corresponding alcohol in these two studies. You conclude based on this information that hydrolysis of the ester bond is unlikely and any differences in toxicological effects due to the formation of different metabolites can be excluded.

ECHA has evaluated this new information. ECHA notes the following deficiencies in your conclusions regarding metabolism of the source and analogue substances. First, the toxicokinetic study on the analogue phosphoric acid, 2-ethylhexyl ester was performed *in vivo* in the rat, whereas the studies on dibutyl phosphate and dimyristyl phosphate were performed *in vitro*. Therefore, these studies are not comparable, and there is uncertainty regarding the potential of the registered substance as well as the analogue substance to undergo metabolism to yield the corresponding alcohols *in vivo*. It is not possible to conclude whether the differences in the results of these studies are due to the differences in the hydrolysis of different phosphate esters, or simply due to the different study designs. Second, ECHA notes that the new *in vitro* studies only measure the appearance of the alcohol peak in that test system, and do not measure the disappearance of the parent phosphate ester. This means that it is possible that the test item is undergoing metabolism to yield different metabolites, but these metabolites are not measured by the test system. It is also possible that the ester bond is undergoing hydrolysis to the corresponding alcohol, and the alcohol itself is metabolised to a different metabolite, and this may account for the absence of the alcohol peak. Therefore, ECHA disagrees with the Registrant's conclusion that hydrolysis of the ester bond can be excluded.
Based on the above, ECHA concludes that you have not sufficiently addressed the structural differences between the target and the source substance and did not explain why those differences would not lead to differences in the toxicity profile of registered and source substances, especially as it relates to the potential formation of different metabolites, which may lead to differences in toxicity between the source and analogue substance in the proposed studies. Given the structural differences between the target and source substances ECHA considers that there is not an adequate basis for predicting the properties of the target substance from source substances.

Toxicological data

Your read-across justification states the following regarding the toxicological similarity of the target and source substances.

"Four different substances (C1, C4 and C16 esters) are used as structural analogue or surrogate for read across purposes. All of them have an unbranched chain between C1 and C16 and exist as a mixture of mono- and diester (with exception of Phosphoric acid, mixed esters with Butyl alcohol and Ethylene glycol) in a comparably concentration ratio. It can also be shown that all four substances are of low acute toxicity demonstrated by an oral LD50 > 2000 mg/kg bw. This is evidenced by a total of 6 valid tests (Reliability 1 and 2) for acute oral toxicity (rat). The genotoxicity potential of these substances, in particular *in vitro* gene mutation in bacteria (5 studies), *in vitro/in vivo* cytogenicity (4 studies) and *in vitro* gene mutation in mammalian cells (3 studies), also show similar results (non-mutagenic/clastogenic). The toxicological profile provided by subacute oral toxicity and reproduction/developmental screening studies proved to be comparable with reference to reproductive issues in case of all Phosphate esters and repeated dose effects in case of the short chain length Phosphate esters (C1 and C4). OECD 422 and 421 studies performed with the four substances showed no effects on fertility and reproductive parameters. The main mode of action observed during the course of repeated dose oral toxicity studies performed with short chain length Phosphate esters is driven by the irritant properties of this class of substances. Commonly observed effects are lesions and/or changes of trachea, forestomach mucosa, and distensions of caecum, duodenum, and jejunum. All these changes are considered to be the result of the local irritant effects of the short chain length Phosphate esters, which have to be classified as irritant or corrosive. No clear systemic toxicity was observed.

Due to the similarity of the chemical structure and functional groups and the comparable study results concerning the toxicological endpoints acute oral toxicity, genotoxicity, reproductive/developmental toxicity and repeated dose oral toxicity a read across between the below mentioned organo phosphate esters is considered to be justified."

According to your explanations both the source and target substances, as well as the other substance cited in your justification document, with the name of reaction mass of phosphoric acid, mixed esters with Bu alc. and ethylene glycol, CAS No 84962-20-9, (EC 284-716-0), have OECD 422 studies available. As mentioned earlier, no endpoint study records in form of (robust) study summaries are available in the registration dossier subject to the present decision for the OECD 422 studies on either the source substance, or the substance with EC number 284-716-0. Nevertheless, this information is available in the respective registration dossiers, and ECHA has used the information in those dossiers in order to aid its assessment of the toxicological similarity.
At the outset, ECHA observes that the studies do show similar effects (mortality/morbidity at the top dose, which is attributed to the irritant properties of the substance) but this occurs at different doses (1000 mg/kg/bw for the source, 450 mg/kg/bw for the target). As indicated in your comments to the draft decision, you consider that these differences are due to the dosing regime (in the source, the doses were 1000, 300, 100, 30, and in the target 450, 120, 50), and do not reflect differences in potency between these studies. In addition to these similarities, ECHA notes that significant differences in toxicity were also seen in these studies. The source substance exhibited effects in the bladder (hyperplasia, degeneration of the epithelium in doses of 100 and above, as well as bladder necrosis in the 100 and 300 groups). These effects were not seen in the study on the target substance. Other effects seen in the source include atrophy of the thymus and spleen (seen in dead animals), as well as vacuolization of the adrenal cortex (seen in dead animals, as well as in animals in the 100 mg/kg/bw dose and above), although these effects were not considered to be significant.

You pointed out that the test sample for the source in this study contains [redacted]% of tributyl phosphate, which is classified as a carcinogen (Hazard class Carc 2 according to Regulation (EC) No 1272/2008), due to effects in the bladder in studies on tributyl phosphate, but the registered substance contains <1% of this impurity. ECHA observes that the presence of such this impurity in the source study complicates the interpretation of this study and the assessment of its relevance for assessing the toxicological similarity between the source and target substances. While the tributyl phosphate impurity may indeed be the cause of the bladder effects, it is not clear if this impurity accounts for the other toxicological differences observed.

Additionally of particular relevance to pre-natal developmental toxicity requested in this decision on the target substance, the OECD 422 study on the source substance resulted in a number of foetuses dying. The results state the following:
"*There were females where all pups in the litter died due to abnormal delivery or abnormality after delivery: 1 such female in the 100 mg/kg bw/d group, 1 in the 300 mg/kg bw/d group and 3 in the 1000 mg/kg bw/d group.*" In contrast, no such effects on the litter were observed in the study on the target substance.

Taken together, these studies may indicate differences in toxicity between the source and target substance that are of relevance to both the 90 day repeated-dose and the pre-natal developmental toxicity study proposals. As the source and target substances display significant differences in toxicity in the OECD 422 studies, ECHA concludes that in this case it is not possible to predict human health effects from data for the reference substance within the group by interpolation to other substances in the group, as required by Annex XI, 1.5.

ECHA has considered your explanation that the bladder effects are likely caused by the presence of the tributyl phosphate ester impurity. However, ECHA notes that while this is one possible explanation for the observed bladder effects, it is not possible, based on the available evidence, to conclude whether these effects are caused only by the presence of the tributyl phosphate ester impurity present in that particular test, or whether other constituents of the source substance contribute to this effect. ECHA considers that in the absence of evidence that allows the exclusion of these bladder effects, these effects clearly demonstrate differences in toxicity among the source and registered substance, and cannot be ignored.
You have proposed that the source substance phosphoric acid, butyl ester CAS No 12788-93-1 (EC No 235-826-2) has similar toxicity regarding sub-chronic toxicity and pre-natal developmental toxicity and therefore the properties of the target substance can be predicted from data obtained from the source substance. You agree with ECHA's consideration that the observed bladder effects create concerns regarding the proposed read-across approach. In your comments to the draft decision, you have also proposed a possible way for addressing these concerns by performing tiered testing, first by performing the studies on the analogue substance, and if these studies show any effects on the bladder, or any effects not typically observed for phosphate esters, to perform the sub-chronic toxicity study and prenatal developmental toxicity study on the registered substance.

ECHA considers that while such a tiered strategy may confirm the your hypothesis, namely that the phosphate esters have similar toxicity, that no differences in toxicity can be expected due to differences in metabolism, and that the bladder effects can be explained by the presence of the tributyl ester impurity. However, ECHA considers that there is sufficient reasons to believe that the properties of the registered substance cannot be predicted from the source substance. These reasons are the differences in toxicity, and the potential differences in metabolism as explained above.

ECHA concludes that:

- the data provided does not provide sufficient evidence to support your hypothesis that the structural differences highlighted in the source and target substances and their possible hydrolysis products do not give rise to a different toxicological profile than that of the source substance, and
- the toxicity profile of the source substance is different from the target substance and therefore, it is not possible to predict the properties of the target substance from the data of the source substance.

ECHA therefore considers that there is not an adequate basis for predicting the properties of the registered substance from the data obtained with the source substance.

One Member State Competent Authority made a Proposal for Amendment for the endpoints of repeated-dose and developmental toxicity, and concerning the basis for read-across. The proposed amendment would (1) note deficiencies in your conclusions regarding metabolism of source and analogue substances (2) suggest that you should consider a read-across based on hydrolysis of the registered and source substances could be more appropriate. In your comments on the Proposal for Amendment, you agree that this approach might be scientifically justified and you agree to perform a read-across to phosphoric acid and the relevant alcohol. ECHA rejected the Proposal for Amendment, since ECHA considers that a read-across hypothesis based on complete hydrolysis/ metabolism of the ester bond is not a reliable basis for predicting the properties of the registered substance, and therefore should not be suggested to you as part of ECHA's decision. Specifically, ECHA notes:

1) The evidence on whether hydrolysis occurs, and the rate at which it occurs, is inconclusive and contradictory. On one hand, the *in vitro* information on hydrolysis of dibutyl phosphate and myristyl phosphate suggests absence of hydrolysis, although this conclusion is not robust for the reasons highlighted above (Section 0.3 under "Structural similarity and dissimilarity, similarity of physico-chemical and environmental fate properties and lack of hydrolysis of the ester bond"). On the other hand, in the *in vivo* hydrolysis / toxicokinetic study on the analogue (phosphoric acid, 2-ethylhexyl ester), hydrolysis was assessed by examining the urine of animals every 12 hours for a total of 72 hours. While complete hydrolysis occurs, this information is not sufficient to exclude that animals are systemically exposed to the parent substance, prior to its metabolism and excretion in urine. As the *in vivo* toxicokinetic study was performed on an analogue substance, it is necessary to consider whether this information can be read-across to the registered substance, especially given the contradictory *in vitro* information. Summarising, there is not adequate evidence to show the metabolism of the source and registered substances in order to support the metabolic read-across proposal and so on this basis the proposal cannot provide a reliable basis for prediction.
2) The metabolic read-across only predicts the properties of the parent substances on the basis that the substances are immediately (or very rapidly) metabolised to the metabolites (phosphate plus alcohol), and that there is no systemic availability of the parent substance. There is no basis for predicting the properties of the parent substance prior to metabolism. In this case, there is no reliable basis for considering that there is no systemic exposure to the parent substance. Consequently, the metabolic read-across hypothesis is not a reliable basis for predicting the properties of the registered substance.

3) The available information on the source and target substances showed some important differences in toxicological properties. These differences are described in this decision (above). This contradicts the predictions of the metabolic read-across hypothesis, and so this is an independent basis for considering that the metabolic read-across hypothesis is not a reliable basis for predicting the properties of the registered substance.
4) As highlighted in the decision, even assuming hydrolysis occurs based on the *in vivo* toxicokinetic study, a metabolic hydrolysis needs to take into account any potential differences in the toxicity of the different metabolites formed as a result of the hydrolysis (e.g. methanol vs. butanol). Information on the hydrolysis products has not been provided, and so there is not a reliable basis for prediction of the properties of the registered substance.

### 0.4 Conclusion on the read-across approach

Based on the data submitted by you, ECHA concludes that you have not provided adequate and reliable information to demonstrate that the read-across approach is plausible for the endpoints in consideration.

ECHA therefore concludes that the criteria of Annex XI, 1.5. are not met, and the read-across approach, as presented by you, cannot be considered plausible to meet the information requirements. Furthermore, ECHA concludes that proposed tiered strategy cannot be considered plausible to meet the information requirements for these endpoints without testing the registered substance, and your proposal for a tiered approach is rejected.

## 1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to EU B.26./OECD TG 408 with the analogue substance phosphoric acid, butyl ester CAS No 12788-93-1 (EC No 235-826-2).

ECHA has evaluated your proposal to perform the test with the analogue substance phosphoric acid, butyl ester CAS No 12788-93-1 (EC No 235-826-2). As explained in Section 0 above, ECHA concludes that the criteria of Annex XI, Section 1.5 are not met, and the read-across approach, as presented by you, cannot be considered plausible to meet the information requirements.

Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA agrees that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration.

More specifically, the substance is a liquid of very low vapour pressure. Uses with industrial and non-industrial spray application are reported in the chemical safety report. However, the reported concentrations are low. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26./OECD TG 408), while your originally proposed test for a sub-chronic toxicity study (90 day), test method EU B.26/OECD TG 408 with the analogue substance phosphoric acid, butyl ester CAS No 12788-93-1 (EC No 235-826-2) is rejected according to Article 40(3)(d) of the REACH Regulation.

**2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species**

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.
A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31./OECD TG 414 by the oral with the analogue substance phosphoric acid, butyl ester CAS No 12788-93-1 (EC No 235-826-2).

ECHA has evaluated your proposal to perform the test with the analogue substance phosphoric acid, butyl ester CAS No 12788-93-1 (EC No 235-826-2). As explained in Section 0 above, ECHA concludes that the criteria of Annex XI, Section 1.5 are not met, and the read-across approach, as presented by you, cannot be considered plausible to meet the information requirements.

ECHA considers that the proposed study performed with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with the rat or rabbit as a first species.

You did not specify the route for testing. ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 40(3) (c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31./OECD TG 414), while your originally proposed test for pre-natal developmental toxicity study in a first species (test method EU B.31/OECD TG 414) with the analogue substance phosphoric acid, butyl ester CAS No 12788-93-1 (EC No 235-826-2) is rejected according to Article 40(3)(d) of the REACH Regulation.

*Notes for your consideration*

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, section R.7.6.2.3.2.

**Appendix 2: Procedural history**

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 8 May 2014.

ECHA held a third party consultation for the testing proposal(s) from 20 May 2015 until 6 July 2015. ECHA did not receive information from third parties.

This decision does not take into account any updates after **3 August 2016,** 30 calendar days after the end of the commenting period.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.
ECHA received proposal(s) for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-54 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

## Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

3. In carrying out the test(s) required by the present decision it is important to ensure that the particular sample of substance tested is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.